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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Davis Wright Tremaine LLP
Barry L Davison
2600 Century Square
1501 Fourth Avenue
Seattle, WA 98101-1688

EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/699,243	MARKL ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4, 7-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4 and 7-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed February 13, 2004. Currently, claims 1-2, 4, 7-15 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

2. Any objections and rejections not reiterated below are hereby withdrawn in view of the amendments to the Claims, applicants' arguments and the 1.132 Declaration filed by Dr. Cathy Lofton-Day.

3. This action contains new grounds of rejection necessitated by amendment.

Maintained Rejections

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 7-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to DNA sequences and methods using DNA sequences selected from CpG island sequences contiguous with or encompassing at least one nucleotide of with SEQ ID NO: 34-37.

The specification describes sequencing 103 "novel" sequences. The specification fails to teach the chromosomal location, the gene, or the cDNA of these DNA sequence fragments. The specification fails to describe contiguous CpG islands of SEQ ID NO: 34-37.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of specifies have been described by their complete structure. In the instant case, Applicant has defined only a fragment of a nucleic acid

sequence. Applicant has not disclosed any genomic DNA sequences and particularly has not disclosed any intron sequences or regulatory sequences. Accordingly, Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus.

Similar to Example 7 of the Written Description guidelines, the specification teaches a fragment of a cDNA or genomic DNA, but does not provide the full cDNA or genomic DNA.

With respect to Claims 7-12, the claimed sequences have not been adequately described. The claims are drawn to a probe or primer which hybridizes to any region of at least 12 contiguous nucleotides from SEQ ID NO: 34-38. The genus of nucleic acids encompassed by the claims is immense. The claims read upon any a probe which hybridizes under low stringency conditions, to a region of 12 nucleotides. This nucleic acid broadly encompasses a nucleic acid with no length limitation which may only have 8-10 nucleotides in common with SEQ ID NO: 34-37. Moreover, where the probe comprises at least 12 nucleotides from SEQ ID NO: 34-37 the nucleic acid broadly reads on the gene from the CpG island was extract, which has not been described. Variants, including polymorphisms, mutations, splice variants, for example. The full length DNA comprising SEQ ID NO: 35-38 has not been described, thus full length genes comprising a smaller portion has not been described.

Response to Arguments

The response traverses the rejection. The response asserts that the claims have been amended requiring that the CpG islands comprise either SEQ ID NO: 36 or 37.

This argument has been thoroughly reviewed, but not persuasive because Claims 7-12 are not limited to SEQ ID NO: 36 and 37. The claims remain drawn to at least 12 nucleotides, as previously argued. The response fails to address this aspect of the rejection. Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-2, 4, 7-12 and Newly added Claims 13-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to a method of diagnosis or prognosis of cancer by performing a methlyation assay to determine a diagnosis.

The specification clearly states that "unfortunately, the mere knowledge of the basic existence of altered methylation of CpG dinucleotides within CpG islands of cancer cells relative to normal cells, or of the fact that in particular instances such methylation changes result in altered gene expression (or chromatin structure or stability), is inadequate to allow for effective diagnostic, prognostic and therapeutic application of this knowledge" (page 2, lines 31-35). The specification continues to state "this is because only a limited number of CpG islands have been characterized,

and thus there is insufficient knowledge, as to which particular CpG islands, among many, are actually involved in, or show significant correlation with cancer or the etiology thereof. Moreover, complex methylation patterns, involving a plurality of methylation-altered DNA sequences, including those that may have the sequence compositions to qualify as CpG islands, may exist in particular cancers" (page 3, lines 1-5). Therefore, there is a need in the art to identify and characterize specific methylation altered DNA sequences, and to correlate them with cancer to allow for their diagnostic, prognostic and therapeutic application (page 3, lines 7-10). The specification teaches the invention provides for 103 DNA sequences having distinct methylation patterns in cancer, as compared to normal tissue (page 5, lines 35-36). These "methylation-altered DNA sequence embodiments correspond to 103 DNA fragments isolated from bladder and prostate cancer patients" (page 6, lines 1-2). Genomic DNA was isolated from tissue of bladder or prostate cancer patients and identified as either hypermethylated or hypomethylated (page 6).

The art clearly illustrates that certain genes, including GSTP1, HIC-1, and p16, are hypermethylated and this is indicative of certain cancers (US Pat. 5,552,277; 5,846,712; 5,856,094).

Neither the specification nor the art teach the skilled artisan how to use the invention as broadly as claimed. First, the specification clearly teaches that "unfortunately, the mere knowledge of the basic existence of altered methylation of CpG dinucleotides within CpG islands of cancer cells relative to normal cells, or of the fact that in particular instances such methylation changes result in altered gene expression

(or chromatin structure or stability), is inadequate to allow for effective diagnostic, prognostic and therapeutic application of this knowledge" (page 2, lines 31-35). The instant specification does not appear to have performed any more experimentation than the mere determination that a basic existence of altered methylation of CpG dinucleotides within CpG islands of cancer cells relative to normal. Therefore, the specification appears to be indicating that this is inadequate to allow for effective diagnostic, prognostic or therapeutic application of this knowledge. In essence, it appears as though the specification teaches that the instant invention is not enabled for use in diagnostic, prognostic or therapeutic applications. In order to use this information, the skilled artisan would be required to sample a population of individuals and assess whether each SEQ ID NO: 34-38 is associated differentially expressed in cancer. This experimentation would be trial and error experimentation which would not have predictable results for the reasons provided in the specification, namely "this is because only a limited number of CpG islands have been characterized, and thus there is insufficient knowledge, as to which particular CpG islands, among many, are actually involved in, or show significant correlation with cancer or the etiology thereof. Moreover, complex methylation patterns, involving a plurality of methylation-altered DNA sequences, including those that may have the sequence compositions to qualify as CpG islands, may exist in particular cancers" (page 3, lines 1-5). In the event that detection of cancer, is not enabled, it is unclear how the polynucleotides may be used.

Second, the specification teaches SEQ ID NO: 36-37 were found to be hypermethylated in a single prostate cancer tissue sample. The specification has

provided a single sample which shows methylation. Thus, the specification does not appear to have performed the analysis implied by the specification to be required for diagnostic and prognostic assays. The specification appears to suggest that more than an existence of hypermethylation of the CpG islands in cancer cells is required. Therefore, based upon the single sample, no predictive prognostic or diagnostic assay appears to be supported.

Third, the indication that one prostate cancer sample indicated a hypermethylation of the region is not indicative that any and all cancers have the same methylation regions. For example, the bladder cancer samples exemplified in the specification do not appear to have hypermethylation of SEQ ID NO: 36-37. Therefore, it is unpredictable whether hypermethylation of SEQ ID NO: 36-37 is a general marker for all cancers, or whether there is a smaller class of cancers which SEQ ID NO: 36-37 are markers, or finally whether the sequence may only be expressed in prostate cancer.

Finally, the specification has not taught that a predictable correlation exists between nucleic acids which are "coordinately methylated contiguous CpG island sequences that comprise a DNA sequence selected from the group consisting of SEQ ID NO: 36-37". The specification has not described any "coordinately methylated contiguous CpG island sequences that comprise a DNA sequence selected from the group consisting ofSEQ ID NO: 36-37", therefore, it is unpredictable that "coordinately methylated contiguous CpG island sequences that comprise a DNA sequence selected from the group consisting of SEQ ID NO: 36-37" are indicative of cancers absent unpredictable and undue experimentation. The skilled artisan would first be required to

determine "coordinately methylated contiguous CpG island sequences that comprise a DNA sequence selected from the group consisting of SEQ ID NO: 36-37" and then assay these unknown sequences to determine whether or not they are hypermethylated or hypomethylated and then whether this aberrant methylation status is associated with cancer. Moreover, the art does not support the idea that all contiguous CpG islands are associated with cancer of prostate, colon or breast. For example, in CACNA1G (see Toyota et al. Cancer Research, Vol. 59, pages 4535-4541, September 1999), a detailed analysis was provided for CpG islands within the gene. The eight regions each behaved very differently. For example Regions 1 and 2 behaved in a concordant manner. Region 3 had either no methylation or very low levels of methylation. Regions 5, 6, 7 behaved differently than regions 1-3. Regions 4, 8 behaved differentially again. Thus, with regards to hypermethylation in cancer, the CpG region upstream of CACNA1G appears to be behave independently (page 4538, col. 1). Therefore, since the art provides examples where CpG islands act in predictable ways (cited by applicant) and examples where CpG islands act independently (cited by examiner, namely Toyota, for example), it is unpredictable whether the instant CpG islands act in a predictable or independent manner. Therefore, it is unpredictable that regions contiguous with SEQ ID NO: 36-37 are associated with cancer.

Therefore, based upon the unpredictability and the undue experimentation which would be required to be performed prior to practicing the full scope of the method, the instant specification has not enabled the instant claims.

Response to Arguments and Declaration filed under 1.132

The response traverses the rejection. The response asserts that the claims have been adequately described. In responding to the examiner's rejection, applicants have set forth several reasons for traversal which will be addressed in the order argued.

The affidavit under 37 CFR 1.132 filed May 23, 2003 is insufficient to overcome the rejection of claims 1-2, 4, 7-12 based upon enablement as set forth in the last Office action. The declaration filed by Dr. Cathy Lofton-Day of May 23, 2003 has been thoroughly reviewed, but found not persuasive to enable the full scope of the instant claims.

First, the claims have been amended to no longer recite prostate cancer association with SEQ ID NO: 36. The claims have been amended to provide an association between SEQ ID NO: 36 and breast or colon cancer. The declaration filed appears teach that two experiments were down, with 35 samples for breast cancer. The declaration does not provide any comparison of these samples to control samples. It is unclear what the statistically significant indication is referring to since there is no data of controls. The specification originally guided the skilled artisan to an association between prostate cancer and SEQ ID NO: 36, however the instant declaration does not make any association. SEQ ID NO: 37 was experimented with prostate cancer. The specification suggested that since SEQ ID NO: 36 was found in a prostate source, there was an association between SEQ ID NO: 36 and prostate cancer. However, it is unclear whether further experimentation determined that SEQ ID NO: 36 was not associated with prostate cancer and taught in the specification. Based upon the unpredictability discussed above, there is no evidence of record to suggest that SEQ ID

NO: 36 is associated with colon cancer. Neither the specification, the declaration or the art provide any evidence of a correlation between hypermethylation of SEQ ID NO: 36 with colon cancer.

Further, Claims 13-15 have been added to diagnose or prognose breast, colon and prostate cancer. The declaration filed appears to teach a single pooled sample and breast cancer. It is unclear whether the pooled sample contained one, two, three or more individual's DNA. It is unclear whether the pooled sample data is significant since it can not be determined whether one of the individual's DNA had a very strong signal whereas three other's had weak signal. Thus, the ability to interpret that pooled sample data is difficult.

The affidavit states that experiments for SEQ ID NO: 36 and 37 have been conducted for breast, prostate and colon cancer. As seen in Table 1, a study of 35 individuals were analyzed for hypermethylation in breast cancer; and SEQ ID NO: 37 was analyzed for hypermethylation in breast, colon and prostate cancers. Moreover, the data is silent with respect to CpG islands which are contiguous with or encompassing at least one nucleotide of SEQ ID NO: 35-38. It is noted that MPEP 2164.05(a), "a showing also must be commensurate with the scope of the claimed invention, i.e., must bear a reasonable correlation to the scope of the claimed invention." The instant showing is not commensurate in scope with the claims, as there is no evidence that hypermethlyation of SEQ ID NO: 36 is associated with colon cancer.

The response asserts that "bladder cancer samples exemplified in the specification are all characterized by hypermethylation of SEQ ID NO: 34-38, as evident

from Table 2." This argument has been thoroughly reviewed, but is not found persuasive because SEQ ID NO: 34-38 are listed as hypermethylated only in prostate cancer. This argument was used to support that hypermethation is not conserved over all cancers. It is noted that the claims do not encompass such limitations, therefore, this argument is moot.

Finally, the response traverses the rejection with respect to the "coordinately methylated contiguous CpG island sequences that comprise a DNA sequence selected from the group consisting of SEQ ID NO: 36-37" within the scope of the claims. The specification teaches that the CpG island sequence associated with the sequence of a particular SEQ ID NO: is that contiguous sequence of genomic DNA that encompasses at least one nucleotide of the particular SEQ ID NO: sequence and satisfies the criteria of having both a frequency of CpG diunucleotides corresponding to an Observed/Expected Ration >0.6, and a GC content >0.5 (page 3, lines 24-28). This argument has been reviewed but is not convincing because the specification has not provided a representative number of associated sequences that comprise SEQ ID NO: 36-37. The specification has not provided a larger portion of a CpG island. Therefore, detecting an associated sequence has not been taught in the specification. Moreover, the art does not support the idea that all contiguous CpG islands or regions comprising at least one nucleotide from SEQ ID NO: 34-38 is associated with cancer of prostate, colon or breast. For example, in CACNA1G (see Toyota et al. Cancer Research, Vol. 59, pages 4535-4541, September 1999), a detailed analysis was provided for CpG islands within the gene. The eight regions each behaved very differently. For example

Regions 1 and 2 behaved in a concordant manner. Region 3 had either no methylation or very low levels of methylation. Regions 5, 6, 7 behaved differently than regions 1-3. Regions 4, 8 behaved differentially again. Thus, with regards to hypermethylation in cancer, the CpG region upstream of CACNA1G appears to be behave independently (page 4538, col. 1). Therefore, since the art provides examples where CpG islands act in predictable ways (cited by applicant) and examples where CpG islands act independently (cited by examiner, namely Toyota, for example), it is unpredictable whether the instant CpG islands act in a predictable or independent manner. Finally, the declaration filed is not commensurate in scope with the instant claims. The declaration filed is directed to SEQ ID NO: 36 and 37. There is no showing of any additional sequences. It is noted that MPEP 2164.05(a), "a showing also must be commensurate with the scope of the claimed invention, i.e., must bear a reasonable correlation to the scope of the claimed invention." Therefore, it is unpredictable that regions contiguous with SEQ ID NO: 36-37 are associated with cancer.

Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

6. No claims allowable.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J. Goldberg

Jeanine Goldberg
Patent Examiner
March 22, 2004

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600